Regeneration of Functional Human Corneal Epithelial Progenitor Cells

Grant Award Details

Regeneration of Functional Human Corneal Epithelial Progenitor Cells

Grant Type: Early Translational II

Grant Number: TR2-01768

Project Objective: The goal of the project is to establish a xenobiotic-free culture system that can efficiently expand human limbal stem cells (LSCs) for transplantation.

Investigator:

Name:	Sophie Deng
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Vision Loss

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $1,524,947

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Regeneration of Functional Human Corneal Epithelial Progenitor Cells

Public Abstract:

Over 3.2 million people worldwide are bilateral blind from corneal diseases. Limbal stem cell deficiency (LSCD) has been recognized as a major cause, either primary or secondary, of significant visual loss and blindness in many common corneal disorders.

A healthy, transparent ocular surface is made up of non-keratinized, stratified squamous epithelium that is highly differentiated. The corneal epithelium is constantly renewed and maintained by the corneal epithelial stem cells, or limbal stem cells (LSCs) that are presumed to reside at the limbus, the junction between the cornea and conjunctiva. When the LSCs are deficient and unable to repopulate the corneal surface, the cornea surface will become opaque. Corneal transplant can't survive and is contraindicated in LSCD.

LSC transplantation, in the form of keratolimbal allograft to restore a transparent corneal surface, has been the main therapy in the United States. The 5-year survival of these allografts is about 30%, largely due to immune rejection. Transplantation of autologous limbal epithelial stem cells that have been expanded on tissue culture has successfully restored vision and revolutionized the patient specific stem-cell based therapy as recently reported by an Italian LSC transplant team. They have achieved a 68% success rate during a mean follow up time of 3 years. The expansion process requires mouse 3T3 feeder cells to grow a sufficient amount of stem cells for transplantation. To reduce cross-contamination from animal products, LSCs that are expanded in a xenobiotic-free culture system has been established; however, the 3-year survival rate of these cells after transplantation is 50% and only 30% survive at 5 year, suggestive of inefficient expansion without the mouse feeders. Therefore, new cell engineering methods that can efficiently expand and regenerate autologous LSCs in a xenobiotic-free system are dearly needed to achieve acceptable clinical outcome and offer stem-cell based therapy to patients with this devastating blinding diseases in the United States.

The first goal of this proposed translational research is to establish a xenobiotic-free culture system by replacing the mouse feeder cells with a human feeder system to expand sufficient amount of LSCs for transplantation. This will allow immediate initiation of clinical trial. We will then further optimized the expansion efficiency by modulating the Wnt and Notch signaling pathways based on our findings that Wnt and Notch signaling regulate the proliferation and differentiation of corneal epithelial cells. In parallel, transdifferentiation of human skin epithelial stem cells to corneal epithelial cells will be induced using a similar approach. The ability and safety of these regenerated human corneal epithelial stem cells to reconstruct the ocular surface will be tested in a LSCD animal model. The results of this proposed study will pave the way for preclinical development of this novel cell engineering technique.

Statement of Benefit to California:	This proposal is to develop a stem-cell based transplantation therapy for treating a blinding corneal disorder, limbal stem cell deficiency (LSCD). Corneal diseases are the second leading cause of treatable blindness in the world and over 3.2 million people worldwide are bilateral blind from corneal diseases. LSCD has been recognized as a major cause, either primary or secondary, of significant visual loss and blindness in many common corneal disorders, such as chemical/thermal burn, keratopathy related to contact lens wear, and severe infection and inflammation. Due to visual impairment, LSCD patients lose the ability to drive, read, and watch TV. In addition, they would experience recurrent corneal erosion that causes severe pain and sensitivity to light. Frequent break down of the corneal surface increases the risk of infection that requires frequent medical interventions. All of these can also exert psychological impact to the patients and their family members. Therefore, LSCD imposes significant social and economical impact on our society. California is the most populated state in the US. There are more than 36 million people in the State of California and the population will increase to 46 million in 2030. Accordingly, the number of residents with limbal stem cell deficiency is likely disproportionately elevated due to the environmental risk factors. Thus, this disease affects a large population of patients in the state of California. A new treatment to restore vision would represent an important benefit to the people of California. Further, the project would train new stem-cell researchers and advance innovative technology in stem cell therapy. This technology has application to other stem-cell related diseases. When this project enters the clinical phase, it will bring together new physicians and scientists and attract funding by the federal government. In addition, it will undoubtedly attract biotechnology investment in California. The stem-cell based transplantation to treat a stem-cell related disease like limbal stem cell deficiency is well-aligned with the broad mission of CIRM and the objectives of the Early Translational Research Award program.